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(21) International Application Number: PCT/IE94/00029 (22) International Filing Date: 16 May 1994 (16.05.94) (71) Applicant (for all designated States except US): BIMEDA RESEARCH AND DEVELOPMENT LIMITED [IE/IE]; Broomhill Road, Tallaght, Dublin 24 (IE). (72) Inventors; and (75) Inventors/Applicants (for US only): CORRIGAN, Owen [IE/IE]; 10 Asgard Park, Howth, County Dublin (IE). MORGAN, James, Patrick [IE/IE]; Bellinter, Navan, County Meath (IE). LOGUE, Paul [IE/IE]; 1 Brighton Mews, Harrison Row, Dublin 6 (IE). O'LEARY, John [IE/IE]; 58 Hampton Park, St Helens Wood, Booterstown, County Dublin (IE). (74) Agents: O'CONNOR, Donal, H. et al.; Cruickshank & Co., 1 Holles Street, Dublin 2 (IE).		(81) Designated States: AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DE (Utility model), DK, DK (Utility model), ES, FI, GB, HU, JP, KP, KR, KZ, LK, LU, LV, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TT, UA, US, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>																		
(54) Title: A VETERINARY COMPOSITION (57) Abstract <p>A veterinary product for treating mastitis in dry cows comprises a first antibiotic-containing composition and a second seal composition in injectors for intramammary application. The antibiotic-containing composition comprises cloxacillin benzathine in a micronised form in an aqueous base. The seal includes a heavy metal salt such as bismuth subnitrate in amounts preferably of greater than 40 %, most preferably 65 % by weight. A gel based on low density or high density polyethylene is used in the seal composition.</p> <div data-bbox="693 1157 1331 1680"> <table border="1"> <caption>Approximate data points from the graph</caption> <thead> <tr> <th>Time (hrs)</th> <th>Cloxacillin (mg/l)</th> </tr> </thead> <tbody> <tr> <td>0</td> <td>1000</td> </tr> <tr> <td>2</td> <td>800</td> </tr> <tr> <td>4</td> <td>600</td> </tr> <tr> <td>6</td> <td>450</td> </tr> <tr> <td>8</td> <td>300</td> </tr> <tr> <td>12</td> <td>150</td> </tr> <tr> <td>24</td> <td>50</td> </tr> <tr> <td>36</td> <td>20</td> </tr> </tbody> </table> </div>			Time (hrs)	Cloxacillin (mg/l)	0	1000	2	800	4	600	6	450	8	300	12	150	24	50	36	20
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0	1000																			
2	800																			
4	600																			
6	450																			
8	300																			
12	150																			
24	50																			
36	20																			

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"A Veterinary Composition"

The invention relates to a veterinary composition, particularly for the prophylaxis and treatment of mastitis in cows.

5 Bacterial infection via the teats of a cow is the most common cause of mastitis.

It is known to treat teats of a cow with a long acting antibiotic with effective cover only being provided whilst minimum inhibitory concentration (MIC) levels of the antibiotic are maintained. This period of cover can vary
10 from 4 to 10 weeks.

It is also known to provide a physical barrier in the teat canal to try to prevent the ingress of pathogens. One such system is described in UK 1,441,747 (Lazonby).

One commercially available barrier system comprises a twin
15 injector pack, one injector containing an antibiotic formulation and a second injector containing a barrier or seal formulation. The antibiotic formulation comprises penicillin salts and dihydrostreptomycin which is infused into the udder following the last lactation and before the
20 cow is dried off. The seal formulation comprises a gel of aluminium stearate and liquid paraffin containing approximately 35% by weight of bismuth subnitrate. This is infused into the udder after the antibiotic formulation to seal the teat canal.

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This invention is therefore directed towards providing an improved veterinary composition for the prophylaxis and treatment of mastitis in dry cows.

5 According to the invention there is provided a veterinary composition comprising an antibacterial formulation, and a seal formulation, the seal formulation comprising a polyethylene gel.

In one embodiment of the invention the gel is based on low density polyethylene.

10 In another embodiment of the invention the gel is based on high density polyethylene.

Typically the gel includes a vehicle such as liquid paraffin.

15 In one embodiment of the invention a non-toxic heavy metal salt is present in the gel base. Preferably, the heavy metal salt is present in an amount of at least 40% by weight of the base, most preferably between 50% and 75%, especially 65% by weight.

Typically the heavy metal salt is bismuth subnitrate.

20 In one embodiment of the invention the antibacterial agent comprises an antibiotic in the form of a substantially insoluble salt in an aqueous suspension. Preferably, the antibiotic agent is a substantially insoluble salt of a synthetic penicillin such as cloxacillin benzathine.

25 Most preferably the antibiotic comprises cloxacillin benzathine.

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Preferably the antibiotic is in a micronised form having an average dimension of less than 25μ . Preferably a substantial proportion of the antibiotic has an average dimension of less than 10μ .

- 5 Preferably the composition is a unit dose. Typically the composition contain 600 mg of cloxacillin as cloxacillin benzathine.

In one arrangement the antibacterial agent is present in the gel base.

- 10 In another arrangement the antibacterial formulation and the seal formulation are separate.

The invention also provides a veterinary composition for use in the prophylaxis or treatment of mammary disorders in non-human animals during an animals' dry period.

15 Detailed Description of the Invention

The invention will be more clearly understood from the following description thereof given by way of example only.

EXAMPLE A

- 20 A veterinary composition comprising a first antibiotic - containing injector (1A) and a second seal-containing injector (2A) were prepared as follows:

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INJECTOR 1A

	Component	g/Kg	Function
	Cloxacillin Benzathine	212.60	Antibiotic
	PVP	0.59	Suspension Aid
5	Sodium Citrate	7.87	Buffer
	Tween 80	0.983	Surfactant
	EDTA (disodium)	0.0787	Cation Scavenger
	Antifoam M30	0.0157	Production Aid
10	Water for Injection	QS	Aqueous Vehicle

* (i) will be adjusted depending on potency

(ii) the cloxacillin benzathine was in a micronised form having an average dimension less than 25 μ with approximately 75% less than 15 μ and 50% less than 10 μ and 85% was greater than 2 μ .

(1) Place most of the water for injection in a production vessel.

(2) Add and dissolve separately, sodium citrate, E.D.T.A., P.V.P. and Tween 80. Mix well.

(3) Add antifoam and mix well, the solution will have a slight haze.

(4) Add and suspend Cloxacillin Benzathine and homogenise for 15 minutes.

(5) Bring to final weight with addition of further water for injection.

(6) Fill 3.6g into intramammary injectors.

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This formulation is stable when subjected to extended storage periods in its proposed marketing container.

We have surprisingly found that cloxacillin benzathine in an aqueous base gives rapid absorption in a very short time period.

A number of studies have been conducted in dry cows to establish the following : -

Study 1: Bioavailability of cloxacillin in bovine colostrum following intramammary infusion of Injector 1A.

Study 2: Residues of cloxacillin in bovine colostrum following intramammary infusion of the first Injector 1A.

Study 3: Irritancy of aqueous cloxacillin in the bovine mammary gland.

The results can be summarised as follows.

INJECTOR 1A - Study 1

A total of 8 cows were infused with Injector 1A and drug levels were measured in colostrum for a period of 144 hours following infusion. A peak of 5233.4 µg/ml was seen one hour post infusion. This declined exponentially and no drug was detectable at 6 days post infusion. The results are presented graphically in Fig. 1. These results are precisely in line with the concept of a teat seal as described herein with a high initial peak effectively sterilizing the udder, with the second Injector providing a barrier to ingress of pathogens

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thereafter. This provides the advantages of reduced risk of drug residues both to the producer and consumer based upon a unique dry cow antibiotic profile.

5 Fig. 1 is a graphic representation of the results of this study.

Fig. 2 is a log transformation of the results of Fig. 1.

These graphs illustrate a linear decline in drug levels over time which is an ideal pharmacokinetic profile.

INJECTOR 1A - Study 2

10 Study 2 was conducted to specifically determine the end point for milk withholding. Animals were infused in each of four quarters with Injector 1A. Samples were taken every 24 hours and analysed for cloxacillin levels. Eight days after administration of the first Injector the levels
15 of drug were below the acceptable maximum residue level for cloxacillin.

INJECTOR 1A - Study 3

This study involved an assessment of the irritancy of the aqueous cloxacillin formulation in the bovine udder. It
20 was found that cloxacillin is mildly irritant in the bovine udder but has no effect on milk yield and the somatic cell count returns to normal 72 hours after infusion.

From these studies it can be concluded that cloxacillin in
25 an aqueous suspension offers a safe and effective means of controlling mastitis in the dry cow and offers significant advantages over existing preparations especially with regard to consumer health and animal welfare.

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EXAMPLE B

A veterinary composition was prepared comprising a first antibiotic-containing injector having the same formulation as Injector 1A described above and a second seal injector 2B as described below.

INJECTOR TYPE 2B

Various gel based on liquid paraffin with polyethylene were prepared. Two grades of polyethylene were used in manufacturing the gels: low density (LDPE) and high density (HDPE). They differed in the degree of side chain branching but produced similar gels.

	Formulation	Mass	Constituents	YV (NM ⁻²)
	2B1	3.5g	3% HDPE - LP gel + 37% BSN + 0.1%Ac	40.9
	2B2	7.0g	3% HDPE - LP gel + 35% BSN + 0.1%Ac	40.9
15	2B3	7.0g	5% HDPE - LP gel + 37% BSN + 0.1%Ac	110.0
	2B4	7.0g	5% HDPE - LP gel + 37% BSN + 0.1%Ac	220.3
	2B5	3.5g	3% HDPE - LP gel + 37% BSN + 0.1%Ac	65.8
	2B6	7.0g	3% HDPE - LP gel + 37% BSN* + 0.1%Ac	36.6
	2B7	7.0g	3% LDPE - LP gel + 37% BSN* + 0.1%Ac	54.1

20 LP = Liquid Paraffin
 BSN= Bismuth Subnitrate
 Ac = Acriflavin
 YV = Yield value - (A measure of the relative fluidity of the gel. Low yield values indicate a more liquid gel).
 25 * = BSN was in micronised form.

Products 2B1 and 2B7 were considered appropriate candidates for use as test seals. An ideal teat seal should have the following characteristics:

30 1. It should be non-irritant to the bovine udder;

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2. Persistence - the seal should remain in situ for the duration of the dry cow period;
3. Consistency - the seal should not break up within the udder;
- 5 4. Compatibility - the seal should be compatible with the antibiotic formulation used in association with it, either aqueous or oily;
- 10 5. Ease of Removal - at the end of the dry period, the seal should be easily removable for the udder and not give rise to persistent residues of either the seal or antibiotic.

Irritancy of the seals was the first characteristic to be assessed as any product which was irritant would have to be rejected irrespective of its performance against the other criteria. Irritancy was measured by conducting somatic cell counts in treated and untreated quarters of lactating cows and comparing these results by measuring area under the curve ratios using the following formula:

$$\text{AUC Ratio} = \frac{\text{AUC of treated quarter}}{\text{AUC of untreated quarter}}$$

This allows for a relative assessment of the various seal formulae.

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	Formulation	AUC RATIO	PEAK (CELLS/mL)	CONDITION OF MILK	DURATION BEFORE RETURN TO PRE- DOSE LEVEL (HOURS)
5	2B1	17.0	5.3×10^6	N	160
	2B2	4.8	2.4×10^6	N	160
	2B3	16.4	$>3 \times 10^6$	N	184
	2B4	3.7	1.7×10^6	N	136
	2B5	10.8	1.0×10^6	N	112
10	2B6	13.0	7.0×10^6	N	120
	2B7	51.8	$>1.0 \times 10^7$	C	112
	N = Normal				
	C = Clotted				

15 Formulations 2B1 and 2B5 were considered appropriate for further investigation. 2B6 and 2B7 (micronised Bismuth Subnitrate) were excluded on the basis of there being more irritant than the other formulas tested and having no significant advantages. Thus, it is concluded that PE-LP gels are viable candidates for sealing teats.

20 In vitro studies have shown that PE-LP gels have high tensile strengths for relatively low yield values. The merits of these two properties were studied by X-ray analysis of various PE-LP formulations in dry cows.

25 A series of studies were undertaken to optimise these parameters:

INJECTOR TYPE 2B - Study 1

	Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm ³	YV NM ²
	2B3	3.1% PE	59.8	0.1	37	7.0	1.32	136.6
30	2B2	1.9% PE	61.0	0.1	37	7.0	1.32	40.0
	2B3'	3.1% PE	59.8	0.1	37	7.0	1.32	220.3

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- PE = Polyethylene
 LP = Liquid Paraffin
 AC = Acriflavin
 BSN= Bismuth Subnitrate
 5 P = Density
 YV = Yield Value
 2B3¹= Formulation is identical to 2B3. Gel was formed using different temperature profile, leading to different yield values.

- 10 Each of the test formulations was infused into quarters of dry cows. The effectiveness of sealing was measured by X-ray analysis. In addition to mass of seal recovered, % BSN recovered and the effective seal duration [ESD] were estimated.

15	Formulation	ESD (days)	Mass of Seal recovered (%)	BSN recovered
	2B3	47.3 ± 16.0	0.62 (8.81)	40.8
	2B2	54.1 ± 10.4	3.00 (43.0)	40.0
	2B3 ¹	49.0 ± 12.9	1.38 (19.7)	44.6

- 20 There was a direct correlation between the ESD and the mass of seal recovered for these products.

INJECTOR TYPE 2B - Study 2

The effect of the product volume and density was examined in another series of X-ray studies.

25	Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm ³	YV NM ²
	2B8	1.7% PE	33.2	0.1	65	5.0	1.70	216.3
	2B9	1.7% PE	33.2	0.1	65	10.0	1.70	216.3

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The results of these studies are shown in table below:

	Formulation	Mass (g) *	% BSN **
		recovered (%)	recovered
5	2B8	3.78 (75.6)	85.6
	2B9	3.92 (39.2)	92.2

* Adjusted for water content

** % BSN were greater than in the previous study indicating a greater integrity of seal. As this trial was of a shorter duration than study 1, this may have been a contributing factor. However, increasing the density and reducing the volume had a clearly beneficial effect on the product performance.

INJECTOR TYPE 2B - Study 3

As it is intended to use the teat seal in conjunction with an antibiotic preparation this study looked at the effect of an aqueous and oily based antibiotic suspension on seal integrity over time. Additionally, the mass of seal was reduced to 3.5g to see if this could further enhance the seals effectiveness.

Products used are given in the table below:

Formulation	Gel former %	LP %	Ac. %	BSN %	Mass g	P g/cm ³	YV NM ²	Anti- biotic
2B8	1.7% PE	33.2	0.1	65	3.5	1.70	2163	Oily
2B9	1.7% PE	33.2	0.1	65	3.5	1.70	2163	Aq.

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The products were then examined for their effective seal duration [ESD].

Formulation	ESD (days)	Recovery of material (g)	BSN Recovery %	BSN Recovery in fluid proportion ppm
5				
B8	56.8 ± 13.9	0	0	1200
B9	60.3 ± 8.2	0.793	77.6	147

A combination of seal and a non aqueous based antibiotic offers a superior combination to seal and an oily based antibiotic. This can be deduced from the fact that the ESD's for the seal/aqueous combinations were significantly better than those for oily combinations. This is further evidenced by the high BSN recoveries (>75%) for the aqueous products, indicating retention of seal in situ.

15 In contrast the amount of bismuth found in the fluid portion at parturition was far lower for the aqueous than the oily combination. This shows that there was a larger degree of dispersal of the seal into the udder with the oily combinations.

20 In conclusion, the use of polyethylene as a gelling agent in combination with heavy metal salts in a teat seal product in combination with an aqueous based antibiotic system provides a product with the desired properties as earlier outlined which should be efficacious in the

25 treatment and prophylaxis of dry cow mastitis.

PREFERRED METHOD OF MANUFACTURE FOR INJECTOR TYPE 2B

	Gm/Kg
H.D.P.E.	17.00
Heavy Liquid Paraffin	332.00
30 Bismuth Subnitrate	650.00
Acridflavin (Pigment)	0.994

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Each injector contains 3.5g.

Bismuth subnitrate ($6\text{Bi}_2\text{O}_3 \cdot 5\text{N}_2\text{O}_5 \cdot 9\text{H}_2\text{O}$) is a white, slightly hygroscopic powder

5 (1) Place heavy liquid paraffin in reactor vessel.
Heat to 160°C for one hour. Cool to 40°C .

(2) Start emulsifiers and mixers and add the H.D.P.E.
Heat to $145^\circ\text{C} \pm 5^\circ\text{C}$ and maintain for one hour.
Cool to 40°C .

10 (3) Add and blend the Bismuth Subnitrate and
Acriflavin.

(4) Fill 3.5g into intramammary injector.

15 In vitro work has shown that polyethylene based gels have tensile strengths and yield values that may make them suitable candidates as sealing agents with low levels or possibly zero levels of heavy metal salts. On such injector type 2C may be prepared as follows:

INJECTOR TYPE 2C

	Polyethylene	30.000
	Liquid Paraffin	969.000
20	Acriflavin	1.000

1) Mix Polyethylene Beads and Liquid Paraffin for 20 minutes.

2) Heat mixture to $140^\circ\text{C} \pm 5^\circ\text{C}$ for one hour with continuous stirring.

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3) Allow to cool to room temperature whilst stirring.

4) Add and blend Acriflavin.

5) Fill 3.5g into intramammary injectors.

5 It has been established that polyethylene which is a pharmaceutically acceptable excipient is capable of being infused by an intramammary injector and has the described rheological properties allowing it to form a seal in situ in the teat canal, particularly in combination with heavy metal salts.

10 The invention is not limited to the embodiments hereinbefore described which may be varied in detail

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CLAIMS

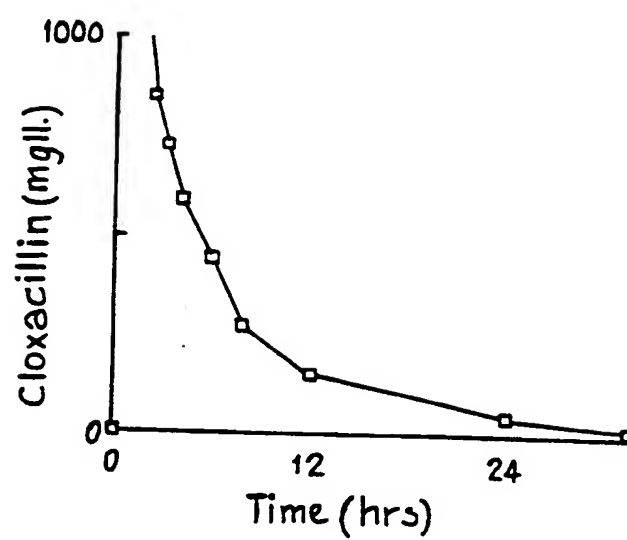
1. A veterinary composition for intramammary use in non-human animals comprising an antibacterial formulation, and a seal formulation, the seal
5 formulation comprising a polyethylene gel.
2. A veterinary composition as claimed in claim 1 wherein the gel is based on low density polyethylene.
3. A veterinary composition as claimed in claim 1 or
10 2 wherein the gel is based on high density polyethylene.
4. A veterinary composition as claimed in any of claims 1 to 3 wherein the gel includes a vehicle such as liquid paraffin.
- 15 5. A veterinary composition as claimed in any of claims 1 to 4 wherein a non-toxic heavy metal salt is present in the gel base.
6. A veterinary composition as claimed in claim 5 wherein the heavy metal salt is present in an
20 amount of at least 40% by weight of the base.
7. A veterinary composition as claimed in claim 6 wherein the heavy metal salt is present in an amount of between 50 and 75% by weight of the base.
- 25 8. A veterinary composition as claimed in claim 7 wherein the heavy metal salt is present in an amount of approximately 65% by weight of the base.

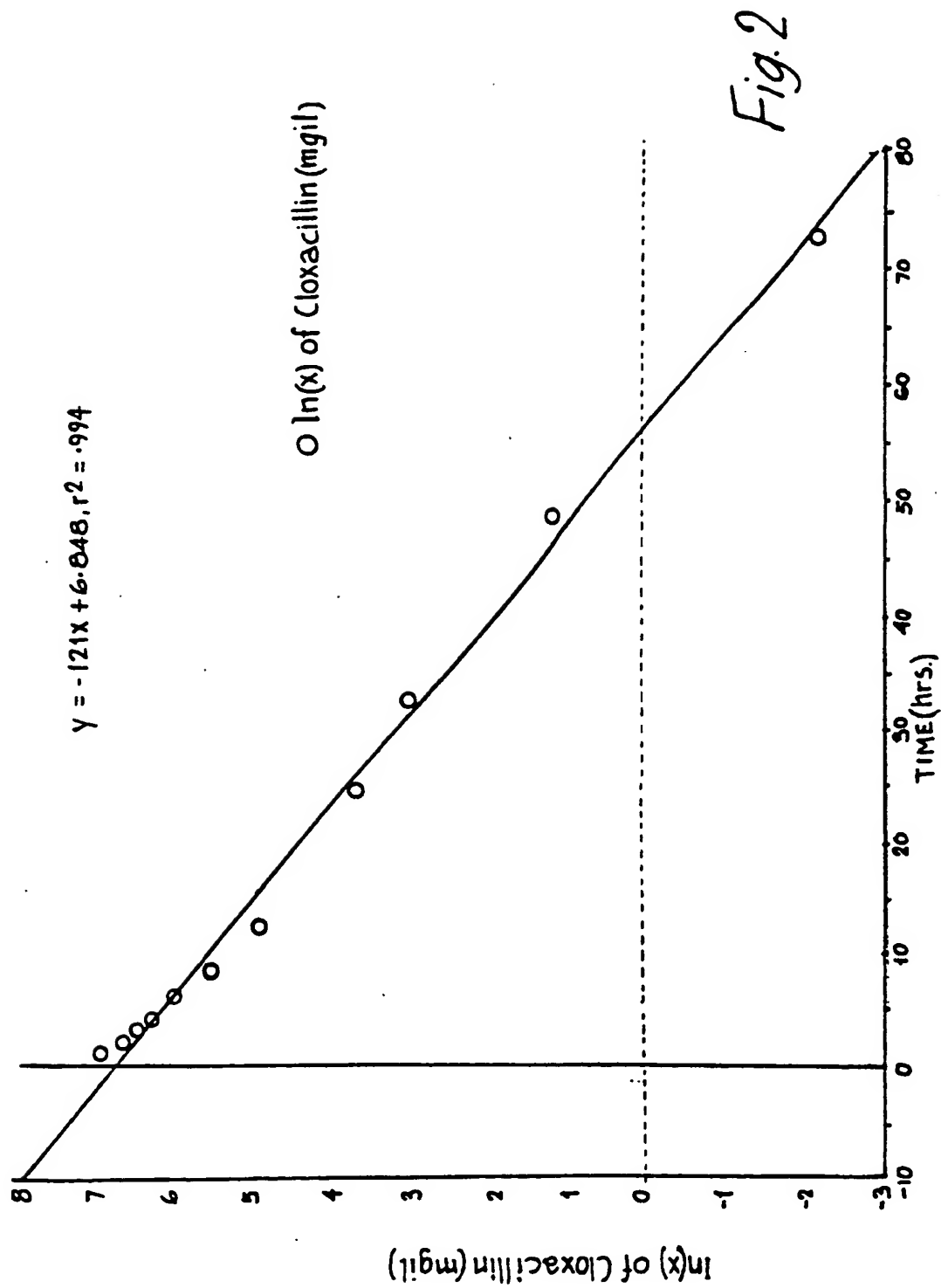
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9. A veterinary composition as claimed in any of claims 5 to 8 wherein the salt is bismuth subnitrate.
- 5 10. A veterinary composition as claimed in any of claims 1 to 9 wherein the antibacterial agent comprises an antibiotic in the form of a substantially insoluble salt in an aqueous suspension.
- 10 11. A veterinary composition as claimed in claim 10 wherein the antibiotic comprises a substantially insoluble salt of a synthetic penicillin.
12. A veterinary composition as claimed in claim 11 wherein the synthetic penicillin is cloxacillin.
- 15 13. A veterinary composition as claimed in claim 10 wherein the antibiotic comprises cloxacillin benzathine.
- 20 14. A veterinary composition as claimed in any of claims 10 to 13 wherein the antibiotic is in a micronised form having an average dimension of less than 25μ .
15. A veterinary composition as claimed in claim 14 wherein a substantial proportion of the antibiotic has an average dimension of less than 10μ .
- 25 16. A veterinary composition as claimed in any of claims 10 to 15 wherein the antibiotic is a unit dose.

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17. A veterinary composition as claimed in claim 16 wherein the composition contains 600 mg of cloxacillin as cloxacillin benzathine.
- 5 18. A veterinary composition as claimed in any preceding claim wherein the antibacterial agent is present in the gel base.
19. A veterinary composition as claimed in claim 1 to 17 wherein the antibacterial formulation and the seal formulation are separate.
- 10 20. A veterinary composition as claimed in any preceding claim for use in the prophylaxis or treatment of mammary disorders in non-human animals during an animals' dry period.
- 15 21. A veterinary composition substantially as hereinbefore described with reference to the drawings and examples.

*Fig. 1*



INTERNATIONAL SEARCH REPORT

Intern al Application No

PCT/IE 94/00029

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

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C. DOCUMENTS CONSIDERED TO BE RELEVANT

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NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+31-70) 340-3016

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Ventura Amat, A

INTERNATIONAL SEARCH REPORT

Information on patent family members

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-2273441	22-06-94	AU-B- 5574294	04-07-94
		GB-A- 2273655	29-06-94
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		WO-A- 9413261	23-06-94

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